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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/727,576	12/05/2003	Praveen Sharma	Q65721	8084

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EXAMINER	
SWITZER, JULIET CAROLINE	
ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
01/12/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/727,576	SHARMA ET AL.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. It is noted that "very early stage breast cancer" is understood to refer to stage 0 breast cancer which includes ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS) (see declaration filed 9/21/07, pages 1 and 2). Thus, the recitation in the claims of "very early stage breast cancer" is interpreted as referring to these two types of cancer.

Claim Rejections - 35 USC § 103

2. Claims 18 and 20-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ralph et al. (US 6,190,857; as cited in IDS) in view of Lukas et al. (Journal of Investigative Medicine, 1997, Vol. 45, No. 1, page 132A).

The rejection is maintained as set forth in the office action mailed 8/18/08.

3. Claims 19, 26, 27, 28, 29, 30, 31, 32, 33, 34, and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ralph et al. in view of Lukas et al. as applied to claims above, and further in view of Wadhwa et al. (Molecular Biotechnology, Volume 6, pages 213-217).

The rejection is maintained as set forth in the office action mailed 8/18/08.

Response to Remarks

Applicant continues to traverse the rejections under 103 and relies upon a second declaration filed by Dr. James Mackay. The arguments and declaration have been fully considered but are not persuasive to overcome the rejection.

Applicant points out that evidence showing there is no reasonable expectation of success may support a conclusion of nonobviousness, and argues that the teachings of Ralph require direct contact between blood and cancer cells to elicit detectable changes. Applicant states that

one of ordinary skill in the art would not have expected to successfully diagnose very early stage breast cancer where no direct contact between the blood cells and disease cells is involved. First, most of the rejected claims are not directed towards diagnosis of very early stage breast cancer, but instead are drawn to methods of screening the blood to identify differentially expressed transcripts that are markers of breast cancer. Further, it is noted, however, that Ralph expressly states that it is expected that detection of markers of disease, and therefor diagnosis of disease using the markers, may be feasible at very early stages of disease when few or no circulating or diseased cells are present in peripheral blood (Col. 5, lines 7-11). Applicant's suggestion that blood cells would not have come in contact with a tumor that does not yet have metastatic potential does not appear to be supported by conventional scientific wisdom. At the time the invention was made, one of ordinary skill in the art certainly would have known that white blood cells spend most of their time outside the circulatory system, patrolling through interstitial fluid and the lymphatic system (Campbell. 1996, page 833). So, it would have been expected that leukocytes would have come in contact with the tumor cells, even if no blood vessels had invaded the tumor.

Applicant points out that Ralph only exemplifies their method with patients who have metastatic cancer which involves direct contact of blood cells with diseased cells. The reference should not be limited only to the teachings of the working examples, but instead should be considered for all that it suggests. Here, Ralph expressly states that their invention is useful for identification of markers for, and detection of, "very early stages of disease," organ defined cancers, and breast cancer. Ralph is clearly suggestive of the application of their method to very early stage breast cancer, however, it is agreed that there is not exemplification of the method for

very early stage or relevant diseases which includes breast cancer. The secondary reference is used to establish that at the time the invention was made there was a desire to identify molecular markers for very early stage breast cancer.

Applicant argues on page 4 that debris or cellular components present in peripheral blood may provide the necessary trigger for the effect observed in Ralph, and that this debris is not seen in very early stage breast cancer. Applicant argues that the office action has not considered the teachings of Ralph as a whole and interpret the statement of Ralph that detection may be feasible at very early stages of disease progression when there are few or no circulating cells present in the peripheral blood "on its own." Applicant argues, as supported by the second Mackay declaration, that one of ordinary skill would have appreciated this and take this disclosure in context with the rest of the teachings of Ralph which is principally concerned with analysis of cancers that have reached metastatic potential or are metastatic. However, the examiner is not taking the teaching of Ralph at Col. 5, lines 5-14 "on their own" but within the entire context of Ralph which is concerned with the novel use of leukocytes as a source of markers for disease. Ralph specifically teaches that their method "relies upon detecting a response to the circulating leukocytes to the disease state" (Col. 5, lines 2-4). Ralph further teaches that the markers can be used to identify disease before individuals exhibit the disease state (such as a tumor), and the methods are suitable for widespread screening of asymptomatic individuals (Col. 14, line 55 and following). Ralph teaches that the method is relevant to organ defined cancers. All of this disclosure would have been understood in light of the state of the art of knowledge regarding the fact that white blood cells spend most of their time outside the circulatory system, patrolling through interstitial fluid and the lymphatic system. Thus, the

examiner's position is not based on reading parts of Ralph "alone" but upon a reading of the entire disclosure read in view of the state of the prior art.

Applicant argues that one of ordinary skill in the art would not have had a reasonable expectation of success of detecting very early stage breast cancer upon the disclosure of Ralph, again relying on the second declaration of Dr. Mackay to support this position. First, it is noted that this argument is not commensurate in scope with all of the claims, the majority of which are directed towards the identification of markers, and not methods for diagnosis of very early stage breast cancer. Absolute expectation of success is not a requirement to establish obviousness of an invention. Here, there was a recognized problem in the art- as supported by Lukas et al.- namely to identify markers for the detection of very early stage breast cancer, and the use of those markers to detect the condition. Ralph provide clear teaching of a method for screening for markers in blood samples, it is undisputed on this record that the molecular biology techniques used by Ralph were routinely employed at the time the invention was made. The contribution provided by Ralph was to look to the blood for the detection of markers of disease at very early stages of disease, diseases which Ralph clearly discloses as including organ defined cancers and breast cancer. One of ordinary skill in the art could have employed the methods of finding the markers in patients having very early stage breast cancer, and, if the markers were present, would have had an excellent chance of success in identifying using the methodologies exemplified by Ralph or other routinely used methods for assay of expression levels of genes in the blood. As noted in the Supreme Court decision KSR, "a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely that product [was] not of innovation but of ordinary skill and common sense. In that

instance the fact that a combination was obvious to try might show that it was obvious under §103." *KSR* 82 USPQ2d at 1397.

In paragraph 15 of the second declaration (filed 12/1/09) Dr. Mackay states that even if one were to consider attempting the claimed invention based on the teachings of Ralph he would not have expected such cancers to be detectable by altered gene expression in blood samples because the cancer cells have not reached metastatic potential and have not released their debris into the blood system. Dr. Mackay refers to the "absence of contact between the blood cells and cancer cells," their components or debris. This is not persuasive because, at the time the invention was made, it was established that blood cells spend most of their time outside the circulatory system, patrolling through interstitial fluid and the lymphatic system. Further, as noted, Dr. Mackay's statements remain in direct contrast to the express teachings of Ralph et al. which teaches "…since the markers are produced by circulating leukocytes rather than diseased cells, it is expected that detection may be feasible at very early stages of disease progression, when there are few of no circulating cells present in the peripheral blood."

On page 6 of the response, as supported by paragraph 18 of the second declaration, applicant notes that while certain portions of Ralph refer to immune detection assays rather than the identification of gene markers, modification of transcript levels acts as a trigger for alteration of antigen levels. While gene expression changes can result in modification of transcript levels, small, observable, levels of gene expression change may not necessarily be detectable at the protein expression level. Thus, Ralph's discussion of immunodetection assays and methods versus gene expression assays are properly separate, and should be considered as such. Applicant further states that the passage at column 52 refers to the effect on "gene expression,"

however, while the passage refers to "expression" it does not in fact refer to "gene" expression, and appears to be referring to the expression of proteins. The examiner is not dismissing the discussion, nonetheless, but considering all of the disclosure, as previously discussed.

Applicant asserts that mere contact between a blood cell and a tumor cell is not enough to allow detection by Ralph, since as asserted in the declaration, the success of the method taught by Ralph is based on "the requirement for the cancer cell to have reached metastatic potential and thus, to display a metastatic phenotype." Ralph never makes this requirement, Applicant has imputed in onto the disclosure of Ralph. In the declaration Dr. Mackay points out that Ralph makes no mention that blood cells that are sampled in the peripheral blood have been altered in terms of their gene expression by contact with tumor cells at the tumor site (paragraph 19). Ralph is not required to disclose the precise mode of action of the gene expression modification. Nonetheless, Ralph does state that their invention is based on detecting a response of circulating blood cells "to the disease state" in conjunction with their statement that there need not be circulating diseased cells present in the peripheral blood. Thus, it appears that Ralph is clearly suggestive that the effect on the blood cells does not necessarily occur due to contact from circulating debris, as applicant asserts. Ralph makes no such requirement, even though applicant and Dr. Mackay repeatedly argue that they do.

Dr. Mackay points to two passages from Ralph et al. to support an assertion that Ralph et al state that direct contact between the sample to be analyzed and the diseased cells is necessary. Both of these passages are in a portion of Ralph et al. that discusses Immunodetection Assays, not the identification of markers based on mRNA expression. When Ralph et al. discuss the identification of markers based on differential mRNA expression, their only qualification for the

sample is that it be a tissue or fluid where leukocytes may be present (Col. 53, lines 1-5). There is no mention that it is required or even preferred that there be direct interaction between cancer cells or their debris or cellular components.

On page 21 of the declaration, Dr. Mackay asserts that "the mere contact of blood cell with a tumor cell is not enough." Suggesting that this would not be sufficient to lead to changes in gene expression in blood samples. However, there is no evidence to support this opinion statement.

Applicant argues, and Dr. Mackay asserts that there is nothing in Ralph that would have guided on of ordinary skill in the art to make the leap to detection of cancers which are phenotypically different and which have not reached metastatic potential (page 7 or response, and paragraph 22 of the second declaration). However, Ralph et al. expressly suggest that their method is relevant to "very early stage" disease (the same language used in the instant claims) and they specifically identify breast cancer as a disease (throughout), and they specifically state that the invention is relevant to metastatic OR organ defined cancers (Col. 10, lines 2-3). Ralph is explicit in providing that their invention is relative to either alternative.

Conclusion

4. No claim is allowed.

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after

the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday or Tuesday from 8:30 AM until 5:00 PM, or on Wednesday from 8:00 AM until 1:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached by calling (571) 272-0731.

The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

7. Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of

the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Juliet C. Switzer/
Primary Examiner
Art Unit 1634

January 9, 2010